REMARKS

Applicants request reconsideration of the above-identified application in view of the foregoing proposed amendments and following remarks.

Applicants have amended withdrawn claims 16-17 and 19-22 to keep their subject matter commensurate with the scope of the pending claims. Applicants have amended claims 23-26 in reply to the Examiner's rejections as detailed below.

Any amendments are made without waiver of applicants' rights to continue to prosecute and obtain claims directed to the former subject matter either in this application or in other applications. None of the proposed amendments presents new matter.

Status of Claims

The Examiner contends that amended claims 16, 17 and 19-22 are drawn to an invention which is independent or distinct from the invention originally claimed. It is the Examiner's position that claims 16, 17 and 19-22, which are directed to method for inhibitor *design*, are directed to a method with different objectives and effect than new claims 23-26, which are directed to method for *identifying* an inhibitor. Thus, the Examiner has withdrawn claims 16, 17 and

19-22 from consideration as being directed to a non-elected invention.

Applicants traverse. According to section 803 of the Manual of Patent Examining Procedure (MPEP), there are two criteria for a proper requirement of restriction between patentably distinct inventions: the inventions must be independent or distinct as claimed and there must be a serious burden on the Examiner if restriction is not required. The MPEP further states that "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to distinct or independent inventions." MPEP § 803.

Applicants believe that it would not be burdensome for the Examiner to search for methods of designing and identifying inhibitors of an unphosphorylated JNK3 as a search of "designing" inhibitors would likely turn up references involving "identifying" inhibitors and vice versa.

For the reasons given above, applicants respectfully request that the Examiner reconsider the withdrawal of claims 16, 17 and 19-22 from consideration.

The Rejections

35 U.S.C. § 112, Second Paragraph: Indefiniteness

Claims 23-26 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. The rejection is detailed below:

3A. The Examiner asserts that in claims 23-26 it is not clear which JNK3 protein is meant because "it is known that there is a plurality of JNK3 proteins." The Examiner also asserts that it is unclear as to which JNK3 protein the particular amino acid residues listed refer. In addition, the Examiner asserts that it is unclear as to why a reference to JNK3 equals JNK3α and points to Davis et al which teaches sequences (in Figures 1A-5B) which have different residues at positions addressed in the instant claims when compared to Figures 2C or 3C. Applicants traverse.

However, solely to expedite prosecution, applicants have amended claims 23-26 to recite an unphosphorylated "JNK3α (c-Jun N-terminal kinase 3α)" molecule rather than an unphosphorylated "JNK3 (c-Jun N-terminal kinase 3)" molecule. Applicants disclose JNK3α1 on page 8, lines 1 to 3; page 10,

lines 10 to 21; and Examples 1 and 2. However, applicants submit that JNK3α has only two isoforms, JNK3α1 and JNK3α2 (see Gupta et al., The EMBO Journal, Vol. 15 No 11, pp. 2760-2770, 1996). Both JNK3 isoforms have identical sequences for amino acid residues 40-402, which are the amino acid residues of the JNK3α1 protein expressed, purified and crystallized in Examples 1 and 2. Given that amino acids 40-402 for both isomers are identical, it would be clear to a person skilled in the art that the instant method could be applied to both JNK3α isoforms.

3B. Claims 23 and 25 are rejected because the phrase "...structure comprising...a JNK3 binding pocket" in claim 23, part a) and claim 25, part c) is allegedly unclear. The Examiner contends that it is not clear: (1) whether the three-dimensional structure generated contains just one pocket; (2) which pocket the phrase refers to; or (3) what type of ligand binds the pocket. Applicants traverse.

The binding pocket in claims 23 and 25 is clear. However, solely to expedite prosecution, applicants have amended claims 23 and 25 to recite a "JNK3α active site binding pocket." Support for this amendment is found on page 9, lines 7-22 of the specification.

In addition, the type of ligand which binds the pocket is clear. Claims 23 and 25 are drawn to a "method for identifying an *inhibitor* of an unphosphorylated JNK3α" (emphasis added). Thus, the ligand which binds the pocket in claims 23 and 25 is an inhibitor.

3C. Claims 23 and 25 are rejected as the recited step of "'employing said three-dimensional structure' is confusing as it does not specify any positive steps involved in the process of 'employing'" (see claim 23, part b and 25, part d). The Examiner alleges that it is unclear what coordinates are being employed as the specification addresses either using all of the JNK3 residues or JNK3-like binding pockets. In addition, the Examiner alleges that the criteria for identifying inhibitors and what constitutes a "JNK3-like binding pocket" is also unclear.

Applicants traverse. The step of employing a three-dimensional structure to design or select a potential agonist or antagonist is described throughout the specification (e.g., see page 18, line 12 to page 21, line 12). The specification teaches that employing the structure relates to evaluating the structure for its ability to associate with chemical entities by, for example, visual inspection or computational analysis.

Thus, given the specification, the steps involved in employing said structure would be clear to one of skill in the art.

3D. Claims 23 and 25 are rejected for lack of antecedent basis as they address "said agonist or antagonist" while the preceding part of the claim does not (see claim 23, part b and 25, part d). Applicants have amended claims 23 and 25 (parts b and d respectively) to recite "said inhibitor" which corresponds with the preceding parts of the claims. Thus, the rejection is obviated.

3E. Claims 23 and 25 are rejected for addressing "said agonist" instead of "said potential antagonist" (see claim 23, part c and claim 25, part e). Applicants have amended, claims 23 and 25 to more particularly point out and distinctly claim the invention. In particular, applicants have amended these claims to recite "potential inhibitors" instead of "agonists or antagonists" or "potential agonists or antagonists." Support for this amendment can be found on page 21, line 28 to page 23, line 11 of the specification. As amended, claims 23 and 25 clearly and correctly recite "potential inhibitor" and "said potential inhibitor."

3F. The Examiner has rejected claims 23 and 25 as the term "ability to interact" is allegedly vague and indefinite. The Examiner asserts that it is not clear how identifying an inhibitor can be achieved by determining its "ability to interact." The Examiner also asserts that the target of the inhibitor is unclear.

Applicants traverse. However, solely to expedite prosecution, applicants have amended claims 23 and 25 to read "ability to associate." Discussions relating to the ability of an entity to bind to, associate with or inhibit a JNK3-like bonding pocket can be found throughout the specification (e.g., see page 10, line 33 to page 11, line 2 and page 21, line 22 to page 22, line 14). The specification teaches that "'associating with' refers to a condition of proximity between a chemical entity or compound, or portions thereof, and a binding pocket or binding site on a protein" and that said association may be either non-covalent or covalent (page 10, line 33 to page 11, line 2 of the specification). The specification also teaches how one would evaluate a chemical entity's ability to associate with a JNK3 (e.g., by using computational means as described on page 22, line 15 to page 23, line 11 of the specification), how to evaluate the efficiency with which it binds a JNK3 after it has been

designed or selected (page 26, lines 1-19 of the specification), and how to optimize it's association with a JNK3 (page 26, line 20 to page 27, line 13 of the specification).

With respect to the Examiner's assertion that the inhibitors target is unclear, claims 23 and 25 recite "identifying an inhibitor *of an unphosphorylated JNK3α*" (emphasis added). Thus, these claims as written identify an unphosphorylated JNK3α as the target of the inhibitor.

In light of the proposed amendments and foregoing remarks in sections 3A-3F above, applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112 rejection for claims 23-26.

35 U.S.C. § 112, First Paragraph: Enablement

Claims 23-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly does not provide enablement for any other JNK3 protein. The Examiner asserts that "the instant claims are directed to [a] method of identifying [an] inhibitor using coordinates of particular amino acid residues located at particular positions of the protein's sequence" and that specification teaches that the

preferred embodiment is JNK3α1. The Examiner additionally states that the working examples are directed to use of JNK3α1. The Examiner again asserts that it is unclear as to why a reference to JNK3 equals JNK3α as Davis et al. teaches sequences (in Figures 1A-5B) which have different residues at positions addressed in the instant claims compared to Figures 2C or 3C. Applicants traverse.

Solely to expedite prosecution, however, applicants have amended claims 23-26. As stated previously, applicants have amended claims 23-26 to recite "JNK3α." Because amino acid residues 40-402 are identical for JNK3α1 and JNK3α2, applicants submit that the instant method could be applied to both known JNK3α isoforms (JNK3α1 and JNK3α2). As amended, claims 23-26 are enabled by the specification. Applicants respectfully request that the Examiner withdraw this rejection.

35 U.S.C. § 103: Obviousness

The Examiner has rejected claims 23-26 under 35 U.S.C. 103(a) for allegedly being unpatentable over United States patent 6,943,000; effective filing date 10/3/1997 ("Davis").

The Examiner asserts that the instant claims 23-26 are directed to a method of identifying a JNK3 inhibitor by generating a three-dimensional structure containing coordinates of binding pocket amino acid residues and using the structure to identify an inhibitor. The Examiner also asserts that claim 25 additionally requires the step of producing the crystal of unphosphorylated JNK3. The Examiner further asserts that: (1) Davis is "directed to the identification and use of JNK3 modulators" and "teaches that computer modeling is used to identify compounds that modulate activity of a JNK3 protein by reacting, for example with its active site"; (2) according to Davis, the active site of JNK3 can be identified using methods known in the art, such as X-ray crystallography, and that once the structure of the active site has been determined, candidate modulating compounds can be identified so that said compounds have structures which match the active site of the structure; (3) the method of Davis is "applicable to any of known JNK3 proteins" and Davis "teaches that there is a plurality of JNK3 proteins known"; (4) while the method disclosed in Davis does not specify the atomic coordinates recited in Figure 1A of the instant invention, that the limitations of these coordinates do not distinguish the instant invention from the prior art in terms

of patentability; and (5) the coordinates in Figure 1A of the instant invention are "descriptive material which alone does not impart functionality either to the data as so structured, or to the computer."

Applicants traverse. Davis discloses a method of screening compounds to identify those that affect expression of a JNK3 gene *or* some other gene involved in regulating the expression of JNK3. Davis also discloses that "the three-dimensional structure of the active site *can be* determined...using known methods, including X-ray crystallography, which *can be* used to determine a complete molecular structure..." and that computer-based modeling *can also be used* to complete an incomplete or inaccurate structure. However, Davis does not meet the requirements for obviousness.

A prima facie showing of obviousness is established by three criteria: (1) some suggestion or motivation in the references or art to modify the reference or to combine reference teachings; (2) some reasonable expectation of success; and (3) a teaching or suggestion of all the claim limitations. Although Davis may suggest that a structure of the active site can be determined, it is well recognized in the art that there is a high degree of unpredictability to

crystallize a protein, to solve the structure of a protein, or to establish the active binding site on a protein. In addition, a large amount of experimentation is needed to do any of the above three steps. Because of the high degree of unpredictability and the large amount of experimentation required, there is no reasonable expectation of success.

In addition, Davis does not include all the claim limitations of claim 25. First, Davis does not teach or suggest with reasonable expectation the steps of producing a crystal of an unphosphorylated JNK3 and determining the three-dimensional atomic coordinates. To the contrary, claims 25 and 26 of the present invention recite these steps. Second, claims 23-26 of the instant invention are drawn to a method for identifying an inhibitor of an unphosphorylated JNK3α which interacts with a defined JNK3α *active site binding pocket*. In contrast to Davis, such an approach does not require the use of the entire JNK3α protein but rather uses a specific set of amino acid coordinates to generate a three-dimensional structure of the JNK3α active site binding pocket against which a potential inhibitor can be designed - a step which is critical to the instant invention.

Furthermore, the Examiner contends that structure coordinates are merely nonfunctional, descriptive matter.

Citing MPEP 2106 Section VI, the Examiner contends that structure coordinates are data. Applicants traverse.

Applicants respectfully submit that structure coordinates are functional descriptive matter. Structure coordinates provide three-dimensional representations of compounds. Contrary to the Examiner's contention that "data" is "merely stored so as to be read or outputted by a computer", drug design involves a person skilled in the art examining, analyzing and interacting with the three-dimensional representation of interest on a computer with use of a graphical screen. MPEP 2106 Section VI cites *In re Gulack*, 703 F.2d 1381, 217 USPQ 401 (Fed. Cir. 1983).

Gulack involves a mathematical device comprising a ring with a plurality of digits printed on the ring and an algorithm by which the digits are developed. The *Gulack* Court held that there was a functional relationship between the printed digits and the ring such that the printed matter must be accorded patentable weight. Hence, if anything, *Gulack* supports the patentability of applicants' pending claims. More particularly, a functional relationship exists between computers and the data stored therein, because the computers convert novel structure coordinates into a display of a novel three-dimensional representation of a binding site for use in

drug design. Such display could not be accomplished without the novel data and the ability of the computer to convert that data into said novel three-dimensional representation.

In *Ngai*, the Fed Circuit affirmed the Board's finding that prior art anticipates a claim because it teaches each and every limitation of the claim and that the only difference between the prior art and the claim is the "*content* of the instructions". The Court found that the content of the instructions was not "functionally related" to the kit, and accordingly concluded that the claim should be rejected as anticipated by prior art. Contrary to *Ngai*, and as stated previously, the alleged prior art Davis does not teach each and every element of claims 25 and 26 of the present invention.

In addition, unlike the instructions in *Ngai*, the structure coordinates are functionally related to the method used to identify or design a JNK3α inhibitor. Contrary to the Examiner's contention that the "atomic coordinates in Figure 1A are merely stored so as to be read or outputted by a computer without creating any functional interrelationship", applicants assert that the coordinates are functionally related to the computer and interact with the computer to produce a unique and novel three-dimensional representation,

which is used as a basis for inhibitor identification or design.

Furthermore, applicants believe this case to be analogous to those cases involving machines that manipulate and convert data in the form of mathematical algorithms into useful, concrete and tangible results. As in those cases, applicants use a special purpose computer - one that displays or produces a three-dimensional representation not previously displayed, because applicants were the first to disclose the novel structure coordinates of JNK3α1. See, e.g., *In re Alappat*, 33 F.3d 1526, 1545, 31 USPQ2d 1545, 1558 (Fed. Cir. 1994) ("[A] general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software" (internal citations omitted)). Without applicants' novel structure coordinates, such display of novel three-dimensional representations of molecular structure for use in inhibitor identification or design would not be possible. The structure coordinates in the present invention produce useful, concrete and tangible results. See *In re Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. Unlike printed matter or music stored in a CD, the structure coordinates are useful only when converted by a computer into a useful, concrete and tangible

result, such as a three-dimensional representation of a novel molecular structure.

For at least the reasons given above, applicants respectfully request that the Examiner withdraw the § 103 rejection.

CONCLUSION

Applicants respectfully request that the Examiner reconsider and withdraw all outstanding objections and rejections, enter the amendments, and pass the resulting claims to allowance.

Respectfully submitted,

Michele A. Kercher

James F. Haley, Jr. (Reg. No. 27,794)
Attorney for Applicants
Michele A. Kercher (Reg. No. 51,869)
Agent for Applicants
FISH & NEAVE IP GROUP
ROPES & GRAY LLP
Customer No. 1473
1211 Avenue of the Americas
New York, New York 10036
Tel.: (212) 596-9000
Fax: (212) 596-9090